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Utilizing Deep Learning and SVM Models for Schizophrenia Detection and Symptom Severity Estimation Through Structural MRI

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ABSTRACT

The automated diagnosis of schizophrenia utilizing Magnetic Resonance Imaging (MRI) has been the subject of numerous investigations, the majority of which have primarily directed their focus towards disorder detection. This study, however, aims to transcend detection, endeavoring to estimate the severity of schizophrenia symptoms by leveraging structural MRI data. Such capabilities are anticipated to enhance the monitoring of treatment efficacy, guide clinical decision-making, and ultimately contribute to improved schizophrenia management. MRI datasets for schizophrenia patients (23) and control subjects (20) were sourced from the OpenNeuro database. Each structural MRI was processed to extract a grayscale image, which was then segmented into White Matter (WM), Gray Matter (GM), and Cerebrospinal Fluid (CSF). Statistical attributes-such as standard deviation, moment, and skewness-were derived from each segment to form feature representations of the grayscale images. An SVM with a linear kernel was trained, distinguishing schizophrenia subjects from healthy controls. Furthermore, for the schizophrenia subjects, the sums of their respective Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) scores were computed. A twelve-layer artificial neural network (ANN) was then trained to estimate these symptom severity scores. The SVM model achieved optimal classification accuracy at 81.8%, while the ANN demonstrated a correlation coefficient of 0.811 and a mean absolute error of 1.44 on the validation dataset. This performance surpasses that of a comparable study estimating schizophrenia symptom severity from electroencephalogram (EEG) data, which yielded correlation coefficients ranging from -0.6 to -0.702. The paper concludes with a proposed software architecture for practical application of these findings.

1. INTRODUCTION

Schizophrenia, a mental disorder typified by hallucinations, delusions, and disordered thinking, typically manifests in adolescence [1-3]. As one of the most prevalent mental disorders, it imposes substantial social disabilities, instigating social, economic, and psychological challenges [1-3]. Astonishingly high mortality rates, including a suicide rate twelve times that of the general population, are associated with schizophrenia [4].

Currently, the diagnosis of schizophrenia relies predominantly on clinical observations and patient interviews, which serve to assess mental status [1, 4]. Guiding this process are two systems: the Diagnostic and Statistical Manual (DSM-IV) and the International Classification of Diseases and Health-Related matters (ICD-10) [4]. However, such observational methods and symptom assessments are inherently subjective, heavily hinging on the clinician's expertise and familiarity with the disorder [2]. Particularly, early differentiation between schizophrenia and bipolar disorder poses a challenge due to shared psychotic symptoms [5]. This underscores the necessity for objective biomarkers that could render diagnoses more consistent, precise, and objective.

Schizophrenia has been observed to correlate with aberrations in brain structure [1, 2]. Studies suggest that schizophrenia patients exhibit decreased grey matter volume in specific brain regions such as the temporal cortex, prefrontal cortex, anterior cingulate cortex, and thalamus [1]. In comparison to healthy individuals, reductions in the grey matter of the fronto-temporolimbic section have been reported in patients with schizophrenia [3]. Structural abnormalities in regions like the middle temporal gyrus and corpus callosum have also been identified [2]. An overall reduction in grey matter is associated with schizophrenia, and these structural changes appear to be linked to the positive symptoms [6].

Structural Magnetic Resonance Imaging (SMRI) can capture these structural changes, making extracted features from such imaging potentially valuable biomarkers for diagnosing schizophrenia [1]. Numerous studies have employed SMRI for differentiating between schizophrenia patients and healthy subjects, typically involving feature extraction from the MRI data and subsequent classification using machine learning algorithms [1, 7]. The highest recorded performance in this field achieved a classification accuracy of 96.7%, utilizing multimodal MRI data and a Support Vector Machine (SVM) [8].

Discriminating between schizophrenia patients and healthy controls is crucial yet insufficient. Estimating the severity of the disorder's symptoms is equally valuable for monitoring treatment responses, particularly to antipsychotic drugs. With quantifiable treatment effectiveness and more precise

decision-making facilitated by this novel capability, clinicians' effectiveness in managing schizophrenia could be significantly enhanced. This study proposes the use of structural MRI for classifying schizophrenia and estimating symptom severity, denoting severity scores by summing the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) from a secondary dataset. The research aims to develop two models: (1) a classification model to distinguish between schizophrenia patients and healthy controls, and (2) a regression model for estimating symptom severity in schizophrenia patients using structural MRI data.

2. REVIEW OF RELATED WORKS

A plethora of studies have been conducted focusing on the deployment of magnetic resonance imaging (MRI) data as neuro-biomarkers to aid in the diagnosis of schizophrenia. Some have utilized multimodal MRI data in their diagnostic procedures. The detection of schizophrenia is typically treated as a classification problem, with the objective being to differentiate between subjects with schizophrenia and healthy controls or non-schizophrenic subjects. Conversely, the estimation of symptom severity is a regression problem. Despite this, a comprehensive review of the literature reveals that the vast majority of research on the use of MRI for schizophrenia diagnosis addresses only the classification problem.

Following preprocessing of the MRI data, the brain is often segmented into Gray Matter (GM), White Matter (WM), and Cerebro-Spinal Fluid (CSF). Subsequently, features are extracted from these three segments, either automatically or manually. This review will delve into studies pertaining to both methods.

Research that incorporates automated feature extraction from MRI data include studies [6, 9], while the majority of the reviewed work involves manual feature extraction from the WM, GM, and CSF segments, including but not limited to studies [1, 7, 8, 10, 11].

In the study conducted by Hu et al. [9], convolutional neural networks (CNNs) were utilized to automatically extract features from GM, WM, and CSF probability maps, subsequently performing classification. The achieved classification accuracy was 79.27%. It is noteworthy that this study also explored manual feature extraction. Alternatively, Oh et al. [6] applied 3D-CNN directly to the raw sMRI images of 443 schizophrenia patients and 423 healthy controls, achieving the highest correct classification rate of 97%. However, when a dataset from a different center was utilized, the performance declined to 71%.

Manual extraction of handcrafted features from sMRI data was employed by the aforementioned study [9] to distinguish 289 schizophrenia subjects from 210 healthy controls. After flattening the GM, WM, and CSF maps and conducting principal component analysis (PCA), support vector machine (SVM) was utilized for classification, resulting in a classification accuracy of 69.15%.

The study conducted by Hu et al. [1] merged GM averages from disparate brain areas with polygenic risk scores obtained from blood samples as genetic characteristics. These features were then used to train an ensemble learning classifier (SVM and logistic regression), resulting in an accuracy of 71.8%. It is noteworthy that this study used a dataset of 508 schizophrenia patients and 502 healthy controls.

In study [7], the Total Intracranial Volume (TIV) was calculated from the MRI images by summing up GM, WM, and CSF segments. This TIV, along with age, sex, and a constant (scanner factor) were leveraged to construct a linear model whose accuracy ranged from 69% to 76%. The dataset encompassed 541 schizophrenia patients and 1252 healthy controls.

Chatterjee et al. [10] utilized a multisite MRI dataset (28 schizophrenia patients and 32 healthy controls) that was preprocessed to focus on grey matter (GM) reduction. Voxel-based morphometry (VBM) analysis was performed on the GM segment for feature extraction. A non-dominated sorting genetic algorithm (NSGA-II) was then used to select fewer features that were combined with age and sex. These features were subsequently used in training an SVM for distinguishing schizophrenia subjects from healthy controls. This methodology achieved a 90% classification accuracy.

In the work conducted by Liu et al. [11], a multitude of markers/features were extracted from MRI and DTI data collected from 62 schizophrenia patients and 33 healthy controls. A two-step feature selection mechanism was introduced to narrow down the most discriminative features, which were subsequently employed to train an SVM classifier. The classifier achieved 91.28% accuracy, 90.85% sensitivity, 92.17% specificity, and an AUC of 0.9485.

The seminal study by Nemoto et al. [7] employed multiple MRI images from 446 schizophrenia patients and 1577 healthy controls, segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The total intracranial volume (TIV) of the region of interest (ROI) was computed by aggregating these segments. The residual value (e) for each participant was then established using a linear analysis with age, sex, TIV, and scanner factor as variables. This residual value was utilized as a distinguishing feature between schizophrenia patients and healthy individuals, achieving an accuracy between 69% and 76%.

In contrast, Yang et al. [8] employed a multimodal MRI dataset, incorporating resting-state functional MRI and structural MRI, derived from 44 schizophrenia patients and 56 healthy controls. An automated anatomical labelling atlas facilitated the extraction of representative features such as grey matter volume (GMV), regional homogeneity (ReHo), the amplitude of low-frequency fluctuation (ALFF), and degree of centrality (DC). The combination of recursive feature elimination and a support vector machine (SVM) facilitated the identification of schizophrenia patients, with the highest accuracy of 96.7% achieved when employing ReHo and ALFF as input features.

Notwithstanding the above, no study to date has ventured to estimate the severity of schizophrenia using MRI data. The current study is poised to address this gap and to develop a comprehensive tool for the detection and monitoring of schizophrenia, thereby providing valuable feedback on patient responsiveness during treatment.

Several established psychiatric rating systems exist for determining the severity of psychiatric syndromes, including the Positive and Negative Symptom Scale (PANSS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Scale for Assessment of Negative Symptoms (SANS) [12, 13]. The PANSS system, for instance, encompasses three major components: positive, negative, and cognitive or general psychopathology scales, each with specific items [13, 14]. The SANS measures negative symptoms across five domains,

while the SAPS assesses positive symptoms.

The only attempt to estimate symptom severity using neuroimaging data was made by study [15], utilizing electroencephalography (EEG) data. The developed regression models displayed correlation coefficients ranging from -0.6 to -0.702 and mean square errors of 3.34 ± 2.40 and 3.9 ± 3.01 for positive and negative symptom severity respectively. The current research is positioned to extend such efforts to MRI data, driving advancements in schizophrenia severity estimation.

3. METHODS

Several studies have been carried out that focus on using magnetic resonance imaging data as neuro-biomarkers for the diagnosis of schizophrenia. There are cases that multimodal MRI was used in the diagnosis.

The methodology is a muti-stage process pipeline with six major stages which are data acquisition, structural MRI preprocessing, extraction of statistical features as the dataset, splitting the dataset into training and test sets, training of the models (classification and regression) and evaluation of the performance of the models. The aforementioned methodology is represented in Figure 1.

3.1 Data acquisition

The neuro-image dataset of schizophrenic and healthy individuals was acquired from Openneuro [16] which was arranged in the Brain Imaging Data Structure (BIDS) standard. It contains structural and functional MRI data of 102 subjects. Importantly, the dataset is de-identified (anonymized) to protect the privacy of the subjects, and this makes it suitable for this research in adhering to ethical research practice.

- The subjects are categorized into four groups:
- Schizophrenia patients (SCZ), twenty-three (23) in total
- Healthy controls (CON), twenty (20) in total
- Schizophrenia patients' siblings (SCZ-SIB), thirty-five (35) in total
- Healthy controls' siblings (CON-SIB), twenty-one (21) in total

This research will primarily focus on the structural MRI (T1w.nii.gz) of the twenty-three (23) Schizophrenia patients (SCZ) and twenty Healthy controls (CON). The pulse sequence of structural MRI (SMRI) is T1-weighted with short repetitive time (TR) and short echo time (TE). The pulse sequence provides contrast between the White Matter (light grey) and the Grey Matter (dark grey) with the Cerebrospinal fluid being dark.

Additional information about the subjects was also provided and this includes gender, age, SAPS and SANS schizophrenia severity scores among several other information. Table 1 shows the demographic distribution of the subjects by gender and age.

Table 1. Statistics of the subjects' count and age distribution

Group		Age
Schizophrenia (23)	Male (17)	23.81 ± 4.73
	Female (6)	25.53 ± 4.71
Control (20)	Male (12)	21.41 ± 4.71
	Female (8)	19.54 ± 4.59

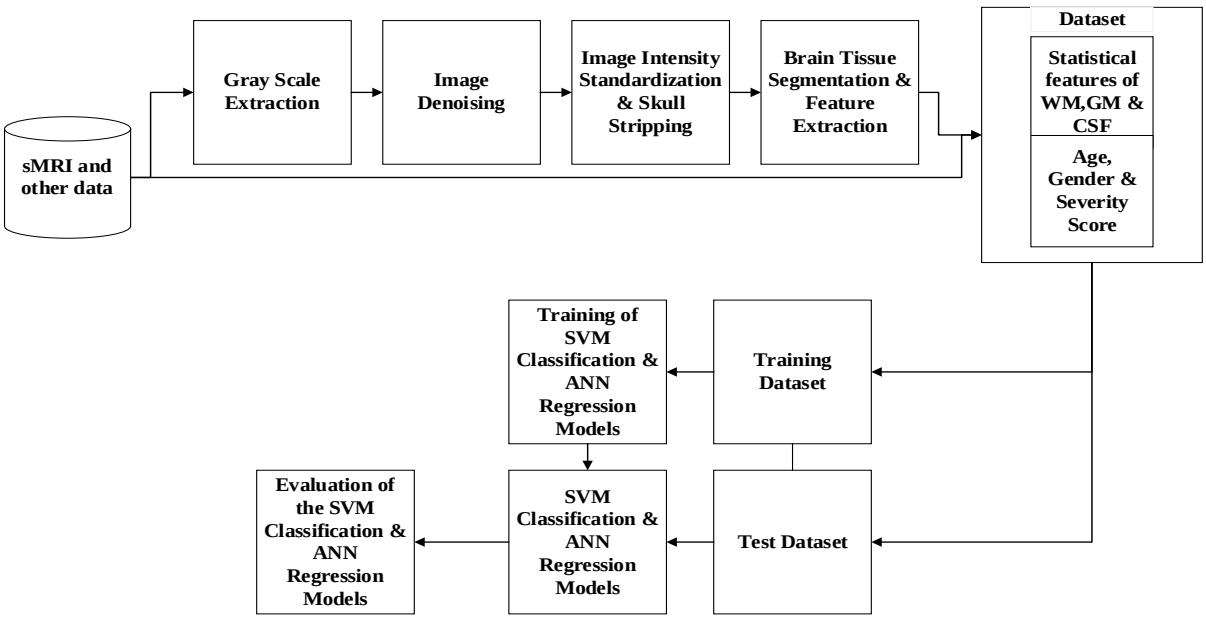

Figure 1. Methods

3.2 MRI image preprocessing

The stage comprises four operations, extraction of greyscale (2D) image from structural magnetic resonance imaging, image denoising or smoothing and image rescaling or standardization.

Extraction of greyscale image: Grey image is extracted from an SMRI file using nibble a python library for processing medical neuroimaging files. The T1-weighted data (*T*1_*data*) has 3-D spatial space with three independent axes *x*, *y* and *z* and has data shape of (*l*, *m*, *n*). A greyscale image *Y* is obtained by taking a slice of the image array of T1_data defined as:

$$Y = T1\_data[:,:,n//2]$$

Image Intensity Standardization: Images from different scanners have different intensities and it is important to these images are standardized. The mathematical representation of this operation is presented in Eq. (1) and computed with NumPy (python numerical library).

$$\text{Standardization}=\frac{I-min\ (I)}{max(I)-\ min\ (I)} * 255 \quad (1)$$

The min(I) and max(I) stand for the minimum and maximum pixel values in the image.

Skull stripping: This is an important part of the preprocessing pipeline as it focuses on the separation of the brain tissue (cerebellum and cortex) from the neighboring region. This process is characterized by a series of operations such as segmentation, binarization and iteration of erosion and dilation morphological process [17]. K-means segmentation algorithm partitions the image into foreground and background. For binarization, the background pixels are assigned a value of zero and the foreground one. The next key operations are dilation and erosion, represented by Eqs. (2)-(3), respectively, which were performed in an appropriate repeated order. The preliminary outcome is the brain tissue mask which is used to mask out the skull from the standardized image to obtain the region of interest. The morphological and segmentation operations are performed with OpenCV, a Python computer vision library.

$$A \oplus B = \{z | B_z \cap A \subseteq A\} \quad (2)$$

$$A \ominus B = \{z | B_z \subseteq A\} \quad (3)$$

A is the image and B is the structuring element.

Brain tissue segmentation: The brain tissue is segmented into four compartments with the Gaussian-mixture model (GMM) from Scikit-learn, a machine learning tool in Python. The compartments are the background, grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The background segment is eliminated from further processing as it does not convey any useful information.

3.3 Feature extraction

Statistical information is extracted from the three-segmented pixel clusters (GM, WM, and CSF), which are the representations for each of the structural magnetic resonance images. The statistical features obtained are standard deviation, entropy, skewness, kurtosis, and moments which are computed using NumPy from the pixel values (v_i) of each of the cluster as represented with Eqs. (4)-(8).

Standard deviation (σ):

$$\sigma^2 = (\left(\frac{1}{n}\right)\sum_i (v_i - u)^2) \quad (4)$$

$$\text{Skewness: } skw\ = \left(\frac{1}{n\sigma^3}\right)\sum_i (v_i - u)^3 \quad (5)$$

$$\text{Entropy: } E = -k\sum_i\ p_i\ log_e\ p_i \quad (6)$$

$$\text{Kurtosis: } Kurt = \left(\frac{1}{n\sigma^4}\right)\sum_i (v_i - u)^4 \quad (7)$$

$$\text{Moment: } m_k = \left(\frac{1}{n}\right)\sum_i (v_i - u)^{\mathrm{k}} \quad (8)$$

A couple of studies have used these statistical parameters extracted from an object's image as its features. The study of Kim et al. [18] shows that these parameters, considered conventional features extracted from EEG, can be used for the classification of schizophrenia, while the Alimi et al. [19] successfully uses the parameters extracted from red blood cells for distinguishing between infected cells and those not infected by malaria parasites. Some of the parameters are also used as acoustic features for discriminating schizophrenia subjects from healthy ones [20].

3.4 Training of classification and regression models

The extracted statistical features are used to train the classifier and regression models. The classifier will learn to differentiate between healthy control subjects and schizophrenia subjects based on the input features extracted from the three segments of the brain (CSF, WM, and GM). An SVM was chosen as the classifier for this study. Recursive feature elimination (RFE) is used to select the seven most important features for segregation between schizophrenia and healthy control datasets before the classifier is trained. The sum of the SAPS and SANS total scores represents the severity of schizophrenia symptoms. An artificial neural network with twelve layers is proposed as the regression model. With regards to the classification problem, 43 data points are used, which are divided into two in the ratio of 75%:25% for training and test sets, respectively. Concerning the regression problem, only data points from the 23 schizophrenia subjects were used, which were divided into training and test sets in a ratio of 75%:25% in favour of the training set.

3.5 Model validation and performance evaluation

After the training of the classifier and the linear regressor, the respective test datasets are used for validation. The performance of the SVM classifier is measured using four metrics, which are accuracy, precision, recall, and F1-score. For the 12-layer ANN regression model, the correlation coefficient and mean square error are considered for its performance evaluation.

4. RESULTS

The acquired data for the research comprises structural magnetic resonance imaging of forty-three (43) subjects (control and schizophrenia groups) and their corresponding age and gender information. The control group consists of twelve (12) males and eight females (8) subjects, while the schizophrenia class consists of seventeen (17) males and six (6) females.

With the extraction of the grey scale image from the BIDS store for each of the subjects, the next operation performed on the image is the normalization to address variations in light intensities from different MRI scanners. Figure 2 shows the image before and after standardization. Also, a 5 by 5 Gaussian kernel was applied to the standardized image to remove noise (smoothing or denoising), and the resultant image is shown in Figure 3.

Skull-stripping is performed with k-means segmentation, binarization, a series of iterative morphological operations, and masking. Figure 4 shows the smoothed image, the mask of the area of interest, and the stripped brain image. In addition, Figure 5 is a gallery of stripped brain images of some of the subjects.

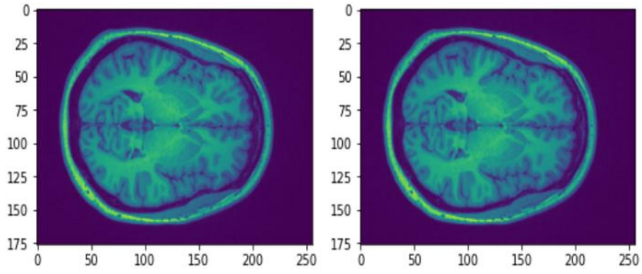

Figure 2. Image before and after standardization

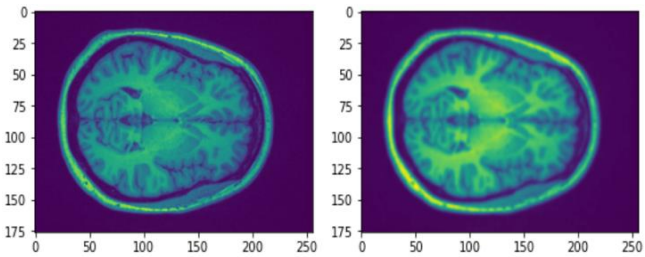

Figure 3. Image before and after the smoothing operation using Gaussian kernel

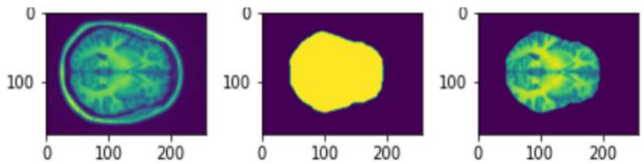

Figure 4. The normalized, smoothed images and the mask of the brain tissue

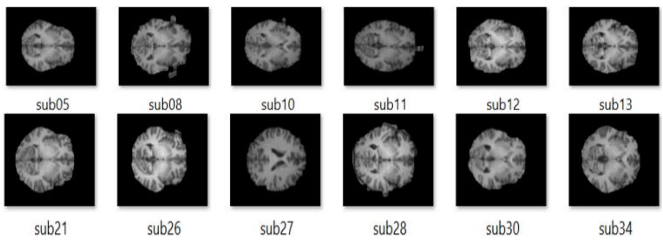

Figure 5. Gallery of some skull-stripped MRI images

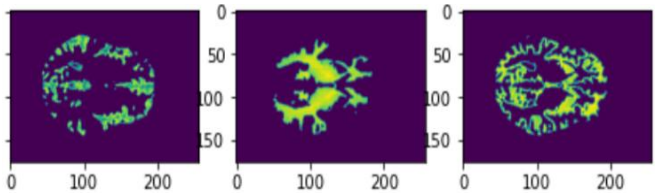

Figure 6. Segmentation of the smoothed image into grey matter, white matter and cerebrospinal fluid

The Gaussian-mixture model (GMM) was used to segment the stripped image into four clusters, the background, the Grey Matter, the White Matter and the Cerebrospinal Fluid, the background cluster is ignored from further processing. The outcome of the segmentation into GM, WM, and CSF is depicted in Figure 6.

Figure 7 shows the histogram of the intensity of cerebral-spinal fluid, grey matter, and white matter segments represented with red, green, and blue colors, respectively, indicating clear separation and effectiveness of the segmentation process. The histogram shows that the higher the intensity or pixel value, the higher the probability of being in the WM cluster, while those with lower values have a higher probability of being in the CSF cluster.

Statistical information such as standard deviation, entropy, skewness, kurtosis, and momentum were obtained from CSF, GM, and WM to form extracted features from the brain tissue segments of each subject. The age and gender information are also included as part of the features representing the subjects. Table 2 shows the dataset with features, also included in the table are the class label and severity scores. The class label 0 denotes the healthy control subject while 1 represents the schizophrenia subject. The schizophrenia symptoms severity scores which is the summation of the SANS total score and SAPS total score.

Figure 8 shows the correlation coefficients of the seventeen extracted features, with the best positive correlation coefficients reported for GM entropy, CSF entropy, CSF standard deviation, and CSF moment with values of 0.224,0.319,0.234 and 0.234 respectively.

The twelve-layer neural network was trained with the training dataset, to predict schizophrenia symptom severity score from the extracted features of the three segments of the brain tissue (GM, WM, and CSF), Figure 9 represents the graph of loss vs iteration number during the training. Five features with the best positive correlation coefficients were selected to build the regression model.

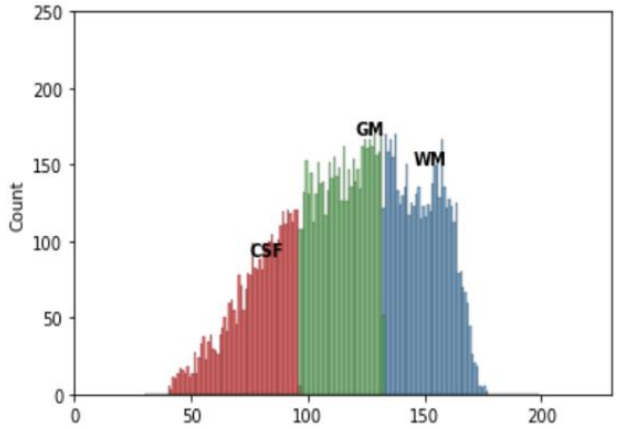

Figure 7. Histograms of brain intensity distribution by tissue class (CSF.GM and WM)

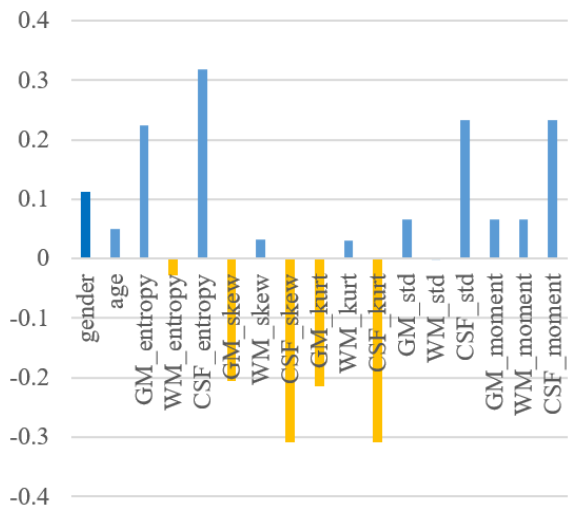

Figure 8. Correlation coefficients of the features and schizophrenia severity score

Table 2. Features extracted from GM, WM and CSF segments and other important information

Participant_ID	Condit	Gender	Age	GM_Entropy	WM_Entropy	CSF_Entropy	GM_Skew
sub-01	1	1	28.961	12.26378	12.72852	13.03354	2.691613
sub-05	1	2	25.6454	11.76337	12.13751	12.37536	3.289669
sub-07	1	2	29.9603	11.80682	12.47576	12.5361	3.3212
sub-09	1	1	23.1157	12.02702	12.34806	12.52394	2.933773
sub-11	0	1	27.5838	12.00111	12.35793	12.58978	2.955976
sub-12	0	2	18.768	11.85462	12.33345	12.66736	3.175685
sub-15	0	1	18.9706	12.17637	12.11962	12.44651	2.710635
sub-17	1	2	25.3771	12.47371	12.49474	11.88929	2.358542
sub-20	0	1	24.8323	11.96066	12.48804	12.4189	3.045928
sub-27	1	1	22.2834	12.04604	12.6131	12.26011	2.914034
sub-31	1	1	24.5749	12.42946	13.01694	12.86257	2.485679
sub-35	0	1	12.6051	12.37117	12.30057	12.68474	2.473272
sub-36	0	1	13.1307	12.57413	12.80382	12.72937	2.260366
sub-37	0	1	14.6092	12.6049	12.34948	12.72825	2.233632
sub-43	0	2	13.8344	12.39658	12.78699	13.16301	2.523116
sub-44	1	1	19.9562	12.35579	12.47026	12.92791	2.522139
sub-46	0	2	15.5099	11.96969	12.39618	12.53991	3.010734
sub-49	0	2	17.2512	12.00598	12.82691	12.77376	3.022601
sub-50	0	1	21.5168	12.30727	12.64311	13.01111	2.61066
sub-54	0	2	20.4025	11.73907	12.05339	12.29319	3.340324
sub-57	0	2	22.9541	12.14335	12.17836	12.32658	2.753877
sub-60	1	1	24.9802	12.24745	13.12724	12.75381	2.682995
sub-62	1	1	20.835	9.595401	13.08953	12.34063	7.533185
sub-64	0	1	22.7105	12.20094	12.92608	13.08893	2.746763
sub-70	1	1	19.6906	12.11621	12.58184	12.88524	2.878077
sub-72	0	1	27.6468	12.35759	12.93961	12.45314	2.532012
sub-74	1	1	19.4579	12.20314	12.72635	12.89215	2.757957
sub-76	1	2	16.1725	12.12464	12.602	12.71963	2.835174
sub-77	1	2	29.7221	12.03648	12.43141	12.48822	2.915327
sub-79	1	1	29.2156	12.15814	12.74276	12.49014	2.806728
sub-81	0	2	24.0329	11.57833	12.61144	12.21913	3.584144
sub-82	1	1	20.7036	11.97128	12.6046	12.61114	3.07267
sub-85	1	1	21.473	8.123896	12.65039	11.83086	12.80303
sub-88	0	1	17.6865	7.565774	12.60962	12.63499	15.60003
sub-91	1	1	23.0746	12.03369	12.96656	12.76931	3.013987
sub-92	1	2	26.2861	5.551898	12.70285	12.43918	31.07688
sub-94	1	1	26.4504	11.98281	12.4255	12.55032	2.992535
sub-95	1	1	27.7728	6.691368	12.73918	12.62031	21.08423
sub-96	1	1	26.0315	9.375612	12.85323	12.29352	8.17902
sub-97	0	2	23.5893	11.82164	12.36482	12.35344	3.200212
sub-99	1	1	26.2177	12.32393	12.88066	12.84452	2.622934
sub-101	0	1	27.9069	11.74004	12.80538	12.54912	3.376228
sub-102	0	1	27.6797	12.46726	12.89205	12.97723	2.409048

Participant_ID	Condit	Gender	WM_Skew	CSF_Skew	GM_Kurt	WM_Kurt	CSF_Kurt
sub-01	1	1	1.985023	1.664887	5.625375	2.010741	0.874765
sub-05	1	2	2.687912	2.404193	9.120774	5.281534	3.864119
sub-07	1	2	2.284033	2.237405	9.536508	3.302552	3.146744
sub-09	1	1	2.431038	2.231216	6.880804	3.98261	3.071991
sub-11	0	1	2.410243	2.144477	6.994258	3.85864	2.66835
sub-12	0	2	2.45376	2.065538	8.391828	4.106116	2.359412
sub-15	0	1	2.710385	2.313825	5.549653	5.401905	3.426481
sub-17	1	2	2.259034	3.060007	3.772621	3.180216	7.605851
sub-20	0	1	2.2596	2.359489	7.619659	3.168865	3.669207
sub-27	1	1	2.106314	2.557381	6.775699	2.482405	4.655326
sub-31	1	1	1.666598	1.855158	4.54157	0.85202	1.551471
sub-35	0	1	2.486544	2.037742	4.320545	4.247953	2.227597
sub-36	0	1	1.904577	2.002929	3.352107	1.709058	2.123538
sub-37	0	1	2.431768	2.003842	3.251137	3.990645	2.125017
sub-43	0	2	1.93041	1.53436	4.727364	1.825502	0.474982
sub-44	1	1	2.286157	1.773638	4.626502	3.302493	1.237416
sub-46	0	2	2.36948	2.210769	7.357092	3.677938	2.976398
sub-49	0	2	1.87586	1.95703	7.533216	1.592919	1.950048
sub-50	0	1	2.089474	1.696708	5.132816	2.452331	0.999641
sub-54	0	2	2.805965	2.515272	9.498311	5.956816	4.43835
sub-57	0	2	2.636091	2.463638	5.792543	5.005786	4.154982
sub-60	1	1	1.539838	1.973392	5.520499	0.429406	2.000313
sub-62	1	1	1.588713	2.630482	55.30403	0.598988	5.374245
sub-64	0	1	1.768428	1.602328	5.882329	1.208019	0.666821

sub-70	1	1	2.154943	1.827423	6.67573	2.718866	1.444613
sub-72	0	1	1.758182	2.304305	4.69582	1.176168	3.381497
sub-74	1	1	1.991945	1.822172	5.98601	2.049448	1.430453
sub-76	1	2	2.133213	2.015109	6.357356	2.629564	2.174868
sub-77	1	2	2.330811	2.266968	6.765263	3.516472	3.216474
sub-79	1	1	1.968295	2.287928	6.23255	1.944068	3.368965
sub-81	0	2	2.115741	2.607577	11.21939	2.540522	4.913155
sub-82	1	1	2.123087	2.138037	7.869415	2.569882	2.681093
sub-85	1	1	2.07612	3.28911	163.9253	2.387369	9.315454
sub-88	0	1	2.114881	2.100576	244.444	2.529592	2.500617
sub-91	1	1	1.722732	1.964015	7.555999	1.044702	1.979462
sub-92	1	2	2.002396	2.328674	966.8913	2.053562	3.508466
sub-94	1	1	2.328989	2.194856	7.241432	3.474183	2.896855
sub-95	1	1	1.969884	2.130251	446.5164	1.944178	2.655247
sub-96	1	1	1.847686	2.67935	65.62735	1.489496	5.618877
sub-97	0	2	2.40312	2.428423	8.516998	3.827371	3.97517
sub-99	1	1	1.815508	1.879332	5.279062	1.368644	1.651719
sub-101	0	1	1.891488	2.203198	9.812996	1.633736	2.949685
sub-102	0	1	1.797209	1.722933	4.107153	1.289614	1.066185

Participant_ID	**Condit**	**Gender**	**WM_Std**	**CSF_Std**	**GM_Moment**	**WM_Moment**	**CSF_Moment**
sub-01	1	1	54.70283	42.45232	436.7411	436.7411	1802.199
sub-05	1	2	45.34751	37.8722	466.2618	466.2618	1434.304
sub-07	1	2	49.20678	35.30661	303.0794	303.0794	1246.557
sub-09	1	1	56.46307	44.46524	689.9869	689.9869	1977.158
sub-11	0	1	39.95149	33.55183	379.3476	379.3476	1125.726
sub-12	0	2	56.01636	46.01071	603.2624	603.2624	2116.986
sub-15	0	1	54.51003	46.4504	910.362	910.362	2157.639
sub-17	1	2	35.95828	38.36526	592.6041	592.6041	1471.893
sub-20	0	1	56.01038	41.31276	560.1405	560.1405	1706.744
sub-27	1	1	47.91075	32.00488	406.4956	406.4956	1024.312
sub-31	1	1	69.08244	47.27261	650.1026	650.1026	2234.7
sub-35	0	1	42.94915	36.56025	532.312	532.312	1336.652
sub-36	0	1	56.25591	39.26871	609.6807	609.6807	1542.031
sub-37	0	1	59.33484	47.96401	888.9289	888.9289	2300.546
sub-43	0	2	53.34031	40.47425	390.2519	390.2519	1638.165
sub-44	1	1	65.39031	54.18927	897.8488	897.8488	2936.477
sub-46	0	2	48.84003	38.4539	484.1048	484.1048	1478.703
sub-49	0	2	65.52571	45.0955	518.1019	518.1019	2033.604
sub-50	0	1	62.54297	47.47646	602.0927	602.0927	2254.014
sub-54	0	2	45.56498	36.52336	430.4714	430.4714	1333.956
sub-57	0	2	49.94759	40.20628	725.0311	725.0311	1616.545
sub-60	1	1	75.32959	48.6925	726.2765	726.2765	2370.96
sub-62	1	1	62.12871	19.82407	14.49107	14.49107	392.9938
sub-64	0	1	52.06992	38.56744	364.6892	364.6892	1487.447
sub-70	1	1	51.37856	40.37275	411.7972	411.7972	1629.959
sub-72	0	1	38.63164	45.47531	440.6541	440.6541	2068.004
sub-74	1	1	58.26906	43.80368	487.2381	487.2381	1918.763
sub-76	1	2	58.9191	43.65753	576.6256	576.6256	1905.98
sub-77	1	2	47.517	38.08298	517.321	517.321	1450.314
sub-79	1	1	50.65068	33.36673	373.8015	373.8015	1113.338
sub-81	0	2	57.08382	37.755	439.3729	439.3729	1425.44
sub-82	1	1	54.35659	40.12008	428.9033	428.9033	1609.621
sub-85	1	1	62.8046	21.84646	7.706772	7.706772	477.268
sub-88	0	1	69.1323	52.65021	7.937528	7.937528	2772.045
sub-91	1	1	74.36122	49.86387	593.3442	593.3442	2486.405
sub-92	1	2	48.84925	34.84938	1.195492	1.195492	1214.479
sub-94	1	1	57.74932	46.61135	714.2899	714.2899	2172.618
sub-95	1	1	51.55567	36.01391	2.013435	2.013435	1297.002
sub-96	1	1	64.26879	22.00471	15.18876	15.18876	484.2071
sub-97	0	2	49.15964	38.40915	514.305	514.305	1475.263
sub-99	1	1	60.21483	41.48608	465.2156	465.2156	1721.095
sub-101	0	1	49.77279	34.72399	318.166	318.166	1205.756
sub-102	0	1	61.45561	45.48675	622.6346	622.6346	2069.044

The test dataset was used to validate the ANN regression model, the predicted severity scores and actual scores are presented in Figure 10.

The correlation coefficient and mean absolute error (MAE) between the predicted scores and the actual scores are 0.811 and 1.44. The correlation value shows that there is a strong relationship between the model output and the actual score, and this is corroborated in Figure 10 as the two regression lines follow the same trend.

For the classification, which refers to being able to distinguish between schizophrenia subjects and healthy subjects, recursive feature elimination (RFE) was used to

select the seven most significant features of the seventeen features. The selected features are age, gender, GM entropy, WM kurtosis, CSF entropy, CSF kurtosis and CSF skewness forming a low-dimensional dataset.

An SVM was trained, and the test dataset was used to validate the classification model. Figure 11 is the confusion matrix representation of the validation output.

Classification accuracy, precision, recall and F1-score computed from the confusion matrix are 81.8%, 87.9%, 81.8% and 82.1% respectively as presented in Figure 12.

It is important to note that the skull stripping operations do not always produce a perfect result, and this occasionally misrepresents the brain clusters (a cluster could be eroded or extended) and can lead to bias in the features extracted from the affected cluster.

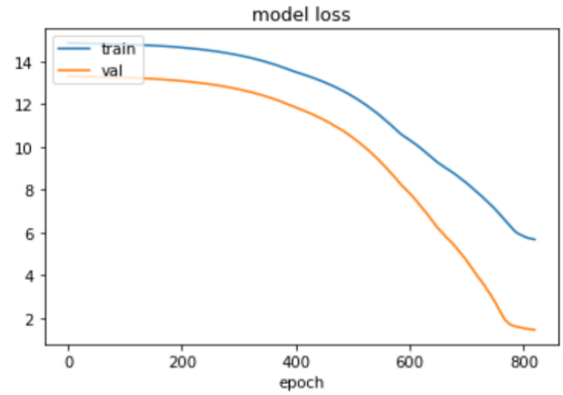

Figure 9. Plot of loss vs iteration number during the ANN regression model training

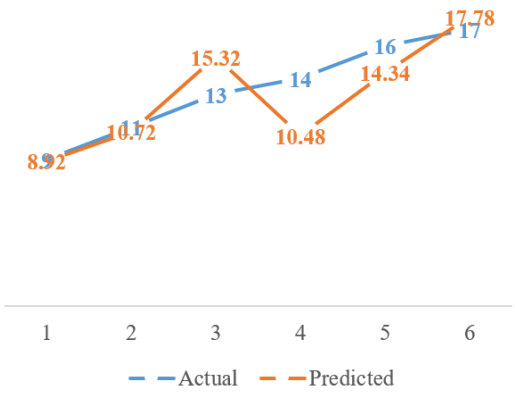

Figure 10. Plot of the actual severity scores and ANN model predicted scores

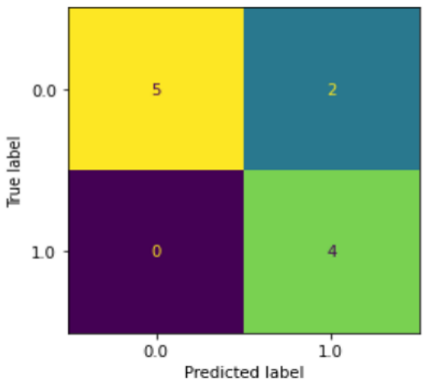

Figure 11. Confusion matrix of the SVM classifier on the test dataset

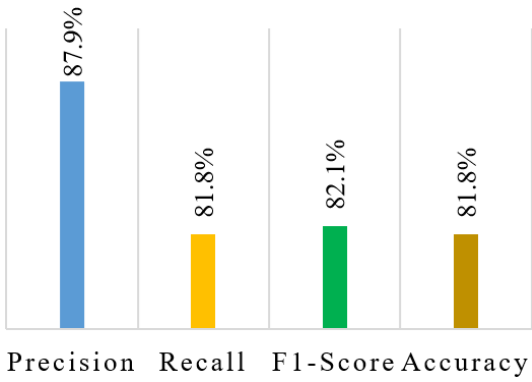

Figure 12. The evaluation outcome of the SVM classifier

5. DISCUSSION

With the extracted statistical features from GM, MW, and CSF segments of the structural magnetic resonance image, the SVM classifier achieved an accuracy of 81.8%and precision of 87.9%. In terms of predicting the symptom severity scores using the summation of SANS and SAPS psychiatric measuring scales, the regression ANN model result was satisfactory with a correlation coefficient of 0.811 between the actual and predicted severity values.

For the regression problem, it was observed that GM entropy, CSF entropy, CSF standard deviation, and CSF moment are the features that had the best positive correlation coefficients with schizophrenia symptom severity; this implies that they are the most significant features in the regression problem and suitable biomarkers for estimating the severity of schizophrenia.

Also, effective biomarkers for the identification of schizophrenia are GM entropy, WM kurtosis, CSF entropy, CSF kurtosis, and CSF skewness based on the obtained results.

Previous studies focused on classification problems, which involve differentiating schizophrenia patients from healthy subjects, while this current work focuses on both classification and regression problems, with more emphasis on the latter being the existing gap being addressed. The classification performance recorded in this research (81.8%) is within the range of what was reported in the previous studies (69.15% to 96.7%). With our regression model, schizophrenia symptom severity can be estimated to a very high degree of accuracy with a 0.811 correlation coefficient to the actual symptom severity scores.

A closely related work developed regression models for estimating schizophrenia symptom severity whose correlation coefficients ranged between -0.6 and -0.702 with EEG data [15]. Our regression model is better for two reasons: (1) It has a positive correlation, and (2) the absolute correlation coefficient is higher (0.811 > 0.702).

Estimating symptom severity is a capability that will help in monitoring treatment effectiveness, assist the clinician in making the right decisions, and lead to an overall improvement in the treatment of schizophrenia.

To make the outcome of this research practically useful, the two models will be integrated with the preprocessing modules as depicted in Figure 13. When the magnetic resonance imaging data is submitted, a greyscale image of the structural magnetic resonance imaging is extracted. It then undergoes an image preprocessing stage that includes standardization, denoising, skull stripping, and segmentation. Statistical

features extracted from the segments of the brain are passed as input to the SVM classifier that determines if the subject has schizophrenia or not. If the subject is not a schizophrenia patient, the flow ends. In a situation when the subject is classified to have schizophrenia, the features are then forwarded to the ANN regression model that estimates the symptom severity score.

The proposed approach in this work produced an outstanding result, but it is important to note that the dataset size of 43 is small; it is therefore advised that the procedure be used on a large dataset for assurance.

It is also recommended to use Deep Reinforcement Learning to drive the morphological operations (repeated series of dilation and erosion) to enhance the results of skull stripping and, inevitably, the quality of the features that are extracted from the three segments (WM, GM, and CSF).

Exploring the combination of structural MRI with other neuroimaging techniques, such as functional MRI, for the possibility of improving the regression model's performance in terms of symptom severity estimation is also encouraged as further research.

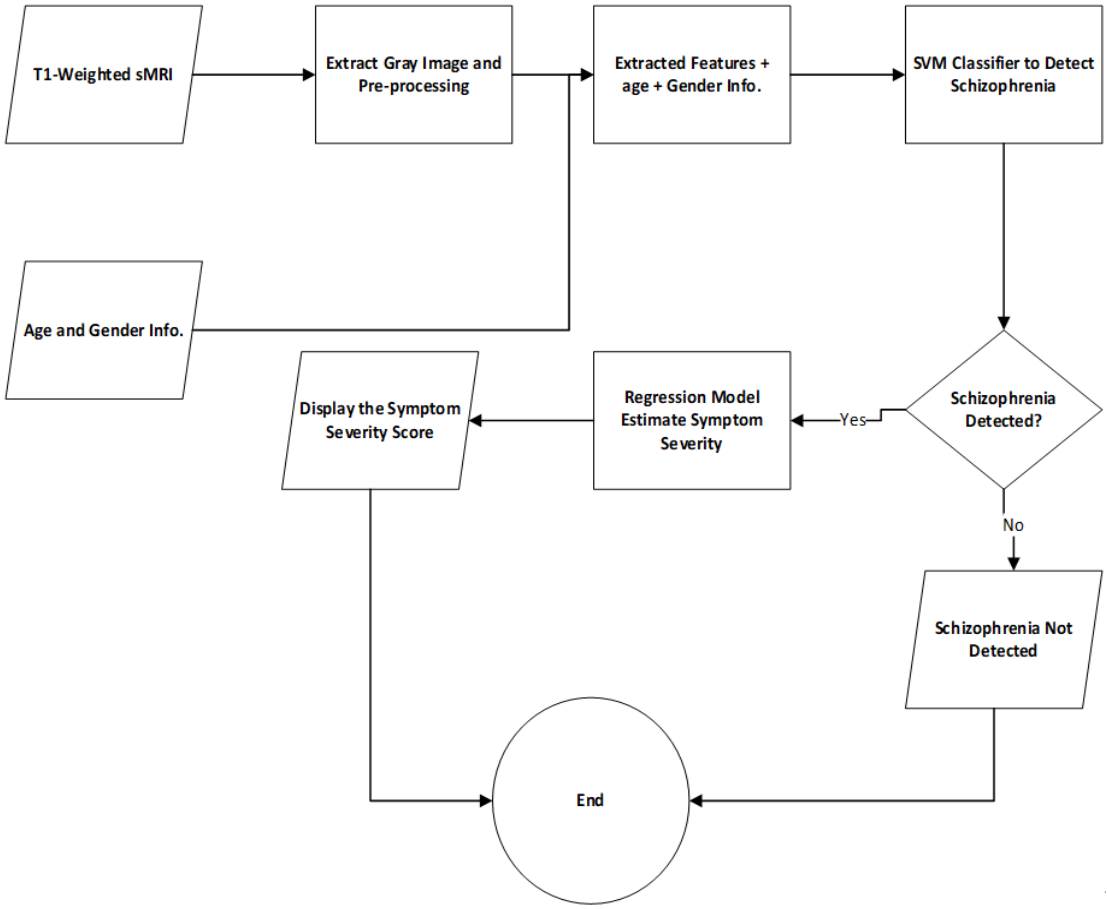

Figure 13. Integrations of the models and preprocessing program for practical use

6. CONCLUSION

The research objectives were achieved. All reviewed previous studies were only concerned with the detection of schizophrenia from MRI data, but with this current work, our state-of-the-art diagnostic models can (1) detect schizophrenia and (2) predict the symptom severity score from structural magnetic resonance imaging data to a very high degree of precision.

We also proposed a software architecture of how the various components developed during this research can be integrated to function as an expert system supporting clinicians in this field.

In conclusion, this regression model for estimating symptom severity will aid in evaluating the efficacy of treatment, guide the physician in making the best decisions which will lead to an overall improvement in the treatment of schizophrenia. The estimation of the severity of schizophrenia symptoms is an area that should be researched further.

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